Restriction

The Examiner states that claims drawn to a non-elected invention are still pending in the application and should be cancelled. Applicants have cancelled claims 54-93 and 113-126 and respectively submit that this objection has been obviated.

Objection to the Specification

The Examiner has objected to the specification because of incorporation by reference to an abandoned application. Applicants have amended the specification to include the relevant material taken from abandoned Application no. 08/005,061. A declaration regarding material incorporated into application has been filed concurrently with this amendment. No new matter has been added. Applicants respectfully submit that this objection has been overcome.

Claim Objections

The Examiner has objected to claims 107-112 as depending from claims that are drawn to non-elected inventions. Applicants have amended claim 107 to remove the dependency from non-elected inventions. Accordingly, it is respectfully submitted that this objection has been overcome.

Rejections under 35 U.S.C.§112, first paragraph

The Examiner has rejected claims 105-107, 109 and 112 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time that the application was filed.

Applicants disagree with this rejection, but have cancelled claims 105, 106, and 112 and amended claims107 and 109 in order to expedite prosecution. Applicants reserve the right to prosecute the subject matter of all these claim in a continuation application. Accordingly, it is respectfully submitted that this objection has been obviated.

Rejections under 35 U.S.C. §112, second paragraph

Claims 101-112 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 101 has been amended to make clearer the claimed invention. Accordingly it is respectfully submitted that this objection has been obviated.

Rejections under 35 U.S.C. §103(a)

Claims 94-104 and 107 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Goelet et al. (WO 92/15712) (hereinafter "Goelet") in view of U.S. Patent No. 5,266,459 to Beutler (hereinafter "Beutler"), U.S. Patent No. 5,429,923 to Seidman et al. (Hereinafter "Seidman"), and Ainsworth et al., Human Genetics, 91, 151-156 (1993) (Hereinafter "Ainsworth").

The Examiner cites Goelet at page 7, third paragraph for the proposition that the method in Goelet permits "one to type or associate 'particular nucleotides,' and then comments that this is the preferred method of the current invention. The Examiner has misread paragraph 3 of page 7 of Goelet. Associate is used in the context of describing related art, as in "problems **associated with the methods** of Mundy and of Vary and Diamond for typing." (emphasis added) See Goelet page 7 lines15-19. Typing in this context refers to sequence determination methodologies wherein the identity of nucleotides at specific positions of nucleic acid molecules are determined.

The Examiner cites page 8 of Goelet as disclosing a method that permits analysis of nucleic acid sequences found to "be useful in the diagnosis of infectious diseases, the diagnosis of genetic disorders, and in the identification of individuals and their parentage." But in Goelet, methods for finding associations between SNPs and traits is not taught or suggested. Nor is genetic mapping using SNPs taught or suggested in Goelet.

Goelet does, as the Examiner indicates, teach genotyping by identification of a specific nucleotide at a defined position, it does not however teach methods of association of SNPs with traits or genetic mapping using SNPs as markers. The Examiner indicates that the methodology disclosed in Goelet can identify genotypes at different genetic loci and with different organisms and discloses the genetic bit analysis.

Applicants however emphasize that the invention as presently claimed is completely independent of any typing or genotyping methodologies. Applicants were the first to recognize that SNPs are pervasively and densely distributed throughout the genome and can be used as markers in genetic maps and for association with traits.

The Examiner cites Beutler as disclosing the association of point mutation with Gaucher's disease and a discussion of allelic frequency. Applicants first point out that Beutler does not discuss allelic frequency. Allelic frequency refers to the proportion of alleles of a particular type at a particular locus (SNP site in this case) out of a group of individuals. Beutler discloses what percentage of disease producing alleles are accounted for by a particular mutation. See for example, Beutler at column 2, lines 2-39. This is distinct from the concept of allelic frequency. Moreover, while Beutler discloses that particular mutation account for disease states, Beutler does not teach or suggest the concepts of associating more than one SNP with disease states regardless of whether any of the SNPs are causative of the trait. Nor does Beutler teach or suggest genetic mapping using SNPs. Butler only adds to the world the finding that particular mutations are causative of Gaucher's disease for different percentages of individuals studied.

The Examiner states that Seidman discloses a process for diagnosing disease caused by multiple genes and multiple point mutations and a diagnostic procedure to determine the likelihood that one having the mutations would develop a disease. The methods in Seidman are premised on the finding that a particular mutation causes a disease state. The invention as presently claimed, by contrast, uses SNPs as markers, for

example, in such applications as genetic mapping or association with traits of interest regardless of whether the SNPs are causative of any disease trait.

The Examiner cites Ainsworth as disclosing the discovery of multiple point mutations, their allelic frequency and the association of the point mutation with the neurofibromatosis (NF1) gene. Applicants have reviewed Ainsworth and do not find any discussion of allelic frequency. The Examiner has again confused the disclosure of whether a mutation causes a certain percentage of diseased patients with the concept of allelic frequency.

None of the references cited by the Examiner describe the association of a plurality of SNPs with traits nor is genetic mapping using SNPs taught or suggested. Beutler, Seidman, and Ainsworth all disclose specific mutations and their causal relationship with disease states. None of these references teach or suggest methods of associating SNPs with traits or mapping using SNPs as markers as in the invention as presently claimed. **Neither do any of the cited references contemplate methods that associate SNP variants with traits by determining whether two or more SNP variants are present in a population of individuals having a trait of interest at allelic frequencies greater than the allelic frequency present in individuals lacking a trait. Allelic frequency is not taught or suggested by any of the cited art, and one skilled in the art would not be motivated from a reading of these references to associate SNP variants with traits of interest based upon a comparison of the allelic frequency of a SNP variant in the population at large with the allelic frequency in a population of individuals having the trait of interest as in the presently claimed invention.**

Applicants respectfully submit that the invention as presently claimed is not taught or suggest by the cited and respectfully request that this rejection has been overcome.

Claims 105 and 106 have been rejected under 35 U.S.C. §103(a) as being unpatentable over the above cited references and further in view of Blum et al. Proc. Nat'l Acad. Sciences 88:5237-5241 (1991).

These claims have been cancelled, as described above, and the Applicants reserve the right to prosecute them in a continuation application. Accordingly, it is respectfully submitted that this rejection has been obviated.

In view of the foregoing Amendment to the claims, and the remarks set forth above, reconsideration and allowance are respectfully solicited.

If any additional fees are determined to be necessary or any overpayment has been made, please charge or credit our Deposit Account No. 11-0171 as appropriate.

If the Examiner has any questions or suggestions of possible amendment for allowance, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Goelet et al

Examiner: Sisson, B.

Serial No.: 08/971,344

Group Art Unit: 1655

Filed: November 17, 1997

Attorney Docket: 13020-2

For: Single Nucleotide Polymorphisms and their use in Genetic Analysis

Kalow & Springut LLP
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New York, NY 10022

Dated: April 17, 2001

Assistant Commissioner for Patents
Washington, DC 20231

MARKED UP PARAGRAPHS IN ACCORDANCE WITH 37 CFR §1.121(b)

Dear Sir:

REMARKS

In accordance with 37 CFR §1.121 (b) the following marked up paragraphs are submitted herewith to accompany the amendment filed concurrently for the application identified above.

At Page 25, line 1: A discussion of the relative advantages and disadvantages of such methods of producing single-stranded molecules is provided by Nikiforov, T. [(U.S. patent application serial no. 08/005,061, herein incorporated by reference).]

Most preferably, such single-stranded molecules will be produced using the methods described by Nikiforov, T. [(U.S. patent application serial no. 08/005,061, herein incorporated by reference).] The invention as described in application serial No. 08/005,061 provides a method for generating single-stranded DNA molecules following a primer-mediated extension or amplification reaction. Such molecules are useful as hybridization probes and in nucleic acid sequencing.

In detail, the invention as described in application serial No. 08/005,061 provides a method for generating a desired single-stranded nucleic acid molecule having a sequence complementary to that of a target nucleic acid molecule, the method comprising the steps:

a) incubating the target molecule in the presence of a primer molecule; wherein the primer molecule is capable of hybridizing to the target molecule, and wherein the primer molecule contains a nucleotide that is substantially incapable of being eliminated by a 5' → 3' exonuclease;

b) permitting template-dependent extension of the primer molecule to thereby form the desired nucleic acid molecule; and

c) incubating the target molecule in the presence of a 5' → 3' exonuclease, wherein the incubation results in the elimination of the target molecule, and thereby generates the desired single-stranded molecule.

The invention as described in application serial No. 08/005,061 additionally concerns the embodiment of the above method wherein step B additionally includes the substep of incubating the desired nucleic acid molecule in the presence of a second primer molecule capable of hybridizing thereto, and of being extended in a template-dependent manner to thereby form a nucleic acid molecule having a sequence substantially complementary to that of the desired molecule.

The invention as described in application serial No. 08/005,061 additionally concerns the embodiment of the above method wherein step B additionally includes the

further substeps of hybridizing the nucleic acid molecule of step B, substep (1), with a complementary primer molecule; and permitting template-dependent extension of the complementary primer molecule to form a nucleic acid molecule having a sequence substantially complementary to that of the target molecule.

The invention as described in application serial No. 08/005,061 additionally concerns the embodiment of the above methods wherein the primer, the phosphorothioate nucleotide derivative, or the single-stranded molecule, or its amplification product is detectably labeled, as with an enzyme label, a fluorescent label, a radioisotopic label, and a chemiluminescent label.

The invention as described in application serial No. 08/005,061 additionally concerns the embodiment of the above methods wherein the desired single-stranded nucleic acid molecule or amplification products are detectably labeled by the incorporation of labeled nucleotides during the template-dependent extension of the primer.

The invention as described in application serial No. 08/005,061 is capable of generating single-stranded molecules regardless of the nature, origin or sequence of the target molecule. Thus, the invention as described in application serial No. 08/005,061 can be used to generate single-stranded molecules that have a naturally occurring sequences, such as a sequence present in a virus (e.g. rhinovirus, hepatitis virus, herpes virus, HIV, etc.), a bacterium (e.g. Escherichia, Clostridium, Mycobacterium, Neisseria, Mycoplasma, Vibrio, Chlamydia, Rickettsia, etc.), a yeast, a fungus, or other lower eukaryote. In particular, the present invention can be used to generate single-stranded molecules that have sequence present in a plant cell, or an animal cell (especially a mammalian cell, such as from a horse, cow, dog, cat or human). The invention as described in application serial No. 08/005,061 can also be used to generate single-stranded molecules that are purely or partially synthetic (i.e. non-naturally occurring). In brief, these methods employ nuclease resistant nucleotides derivatives, and incorporates

such derivatives, by chemical synthesis or enzymatic means, into primer molecules, or their extension products, in place of naturally occurring nucleotides.

At page 51, line 13: To obtain single-stranded template for use with solid phase immobilized primer, either of two methods may be used. [First, the amplification may be mediated using primers that contain 4 posphorothioate-nucleotide derivatives, as taught by Nikiforov, T. (U.S. patent application serial no. 08/005,061).] First, the amplification may be mediated using primers that contain 4 phosphorothioate-nucleotide derivatives. Alternatively, a second round of PCR may be performed using "asymmetric" primer concentrations.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Goelet et al

Examiner: Sisson, B.

Serial No.: 08/971,344

Group Art Unit: 1634

Filed: December 21, 1999

Attorney Docket: 13020-2

For: Single Nucleotide Polymorphisms and their use in Genetic Analysis

Kalow & Springut LLP
488 Madison Avenue, 19thFloor
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Dated: April 17, 2001

Assistant Commissioner for Patents
Washington, DC 20231

MARKED UP CLAIMS IN ACCORDANCE WITH 37 CFR §1.121(c)

Dear Sir:

REMARKS

In accordance with 37 CFR §1.121 (c) the following marked up claims are submitted herewith to accompany the amendment filed concurrently for the application identified above.

94. (Amended) A method of generating a genetic map of an individual, comprising:

(a) providing a [single nucleotide polymorphism (SNP) marker set which comprises] polymorphic array comprising three or more single nucleotide polymorphisms

(SNPs), wherein each [allele] SNP variant in the polymorphic array has an allelic [frequencies between 0.001 and 0.999] frequency of at least 0.20;

(b) identifying the [alleles] SNP variants present in an ancestor of the individual by determining the base identity at each SNP site of the ancestor of the individual and identifying the [alleles] SNP variants present in the individual by determining the base identity at each SNP site of the individual;

(c) determining the number of matches between the individual and the ancestor[;],

(d) calculating the extent of genetic linkage between each allele from the number of matches of step (c) and the probability that any pair of alleles found in the individual were inherited from the same ancestor based on the allelic frequencies [in the reference marker set] of the SNP variants of the polymorphic array, thereby generating the genetic map of the individual.

99. A method for determining the probability that a target individual will have a particular trait, comprising:

(a) identifying a single nucleotide present at a polymorphic site of a single nucleotide polymorphism, wherein the single nucleotide is present in more than 51% of a set of reference individuals;

(b) determining whether a single nucleotide present at a polymorphic site of a corresponding single nucleotide polymorphism of the target individual has the same identity as the single nucleotide present at the polymorphic site of the 51% of reference individuals exhibiting the trait, and

(c) determining the probability that the target individual of step (b) will have the particular trait.

100. A method according to claim 99, wherein the trait is a genetic disease.

101. (Amended) A method of associating the presence of a particular trait of interest found in a[n] population of individuals with [a particular allele found at a SNP site] two or more SNP variants, comprising:

(a) selecting two or more SNP sites wherein each [allele] of the SNP variants has a known allelic frequency and does not cause the trait [has an allelic frequency between 0.001 and 0.999];

(b) identifying the [alleles] SNP variants present in [one or more] each individual[s] having the trait of interest by determining the base identity at each SNP site, and

(c) determining whether [one] two or more [alleles] SNP variants are present in the population of individuals having the trait of interest at [a frequency] frequencies greater than the allelic frequency present in individuals lacking the trait, thus associating the [alleles] two or more SNP variants with the trait of interest.

102. (Amended) A method according to claim 101, wherein each [allele] SNP variant has an allelic frequency [between 0.01 and 0.99] of at least 0.20.

107. (Amended) A method according to claims [83, 91,] 94[, 99] or 101, wherein the individual [or target individual] is selected from the group consisting of animals[,] and plants[, fungi, yeast and C. elegans].

108. (Amended) A method according to claim 107, wherein the individual [or the target individual] is a mammal.

109. (Amended) A method according to claim 108, wherein the mammal is selected from the group consisting of human, non-human primates, dogs, cats, cattle, sheep[,] and horses[, mouse, rat and rabbit].

110. (Amended) A method according to claim 108, wherein the individual [or target individual] is a human.

111. (Amended) A method according to claim 108, wherein the individual [or target individual] is a horse.

Respectfully submitted,

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